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Nonsustained effect of short-term bisphosphonate therapy on bone turnover three years after renal transplantation

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Background. We recently showed that two doses of 4 mg of zoledronic acid (ZOL) ameliorated the bone loss and improved bone histology within the first six months after kidney transplantation. The aim of the present study was to evaluate whether this early short-term intervention exhibited a sustained bone-sparing effect.

Methods. A homogenous group of 20 de novo renal transplant recipients were equally randomized to two infusions of 4 mg of ZOL or placebo at two weeks and three months after engraftment. Patients were followed up for three years by sequential determination of bone densitometry and specific biochemical markers.

Results. From month six to three years after transplantation, both treatment groups exhibited an improvement of bone mineralization. Femoral neck bone mineral density z-scores increased statistically significantly from −1.3 (2.6) to −0.2 (3.6) in the placebo group and from −1.6 (2.9) to −1.2 (1.9) in the ZOL group (median, range). Biochemical parameters of osteoblast activity such as osteocalcin and bone-specific alkaline phosphatase did not increase significantly in both groups. Osteoprotegerin, a marker of osteoclast inhibition, was significantly elevated over the first six months in the ZOL group, but decreased to similar levels, as in the placebo group, over the next two and a half years. Other markers of osteoclast activity such as c-telopeptide of type 1 collagen, calcitonin, and intact parathyroid hormone were not different between six months and three years in either group.

Conclusion. The early bone-sparing effect of short-term ZOL therapy confers no sustained benefit versus placebo at three year post-transplantation.

Post-transplant osteodystrophy remains a major enigma after solid organ transplantation. The fracture rate in the first two years is reported to average 10% in renal transplant recipients and is even higher in heart and lung transplant recipients [1, 2]. The cumulative fracture rate in patients transplanted more than five years averages 44% [3]. The reasons for the high incidences are many, but corticosteroid therapy has been shown to be the main contributor [4]. The most severe loss of bone mineralization density occurs within the first months after transplantation. Julian et al [5] reported a loss of bone mineral density (BMD) in lumbar spine of almost 10% within the first six to 18 months after transplantation [5]. This is the time frame when corticosteroid doses, used for maintenance immunosuppression and to treat rejections, are highest. Cumulative doses of roughly 5 to 10 g within the first six months are standard in many centers. Only recently, corticosteroid sparing or elimination regimens are being evaluated in selected patients [6, 7]. Because complete elimination of steroids is not recommendable for most of the patients and calcineurin inhibitors have also been shown to cause bone disease, post-transplant osteodystrophy will also be a problem in the near future. Besides bone specific side effects of immunosuppression, hyperparathyroidism is another main contributor to osteodystrophy, especially in renal transplant patients [8]. Hyperparathyroidism causes high turnover bone disease, which is functionally characterized by excessive activation of osteoblasts and osteoclasts. The secondary hyperparathyroidism usually subnormalizes within the first weeks after successful renal transplantation, when conversion of 24,25 to $1,25(OH)_2$ vitamin D_3 functions properly, as does enteral calcium resorption and renal phosphate elimination.

In general, bone loss in the first months after transplantation is well recognized, but conflicting data exist on long-term bone turnover in patients after successful renal transplantation. We recently showed that short-term treatment of renal transplant recipients with two injections of low dose zoledronic acid (ZOL), a third generation bisphosphonate, at two weeks and three months after engraftment could prevent the loss of bone

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Table 1. Cumulative or daily doses of drugs known to influence bone turnover/mineralization

	Placebo $N = 10$			ZOL $N = 9$		
	0 to 6 months	7 months to 3 years	*P* value	0 to 6 months	7 months to 3 years	*P* value
Cumulative CSA dose *g/6 months*	45 (25)	32 (18)	0.012	43 (59)	30 (54)	0.018
Cumulative steroid dose *g/6 months*	2.9 (4.5)	1 (0.7)	0.005	2.9 (1.4)	0.7 (1.1)	0.008
Average dose of loop diuretics *mg/day*	0 (80)	0 (40)	0.28	0 (80)	0 (80)	1.0
Average dose of thiazide diuretics *mg/day*	0 (25)	0 (12.5)	0.66	0 (12.5)	0 (12.5)	1.0
Average dose of 1,25$(OH)_2$ vitamin D_3 *μg/day*	0 (0)	0 (0.25)	0.18	0 (0)	0.13 (0.5)	0.039
Average dose of calcium supplementation *g/day*	1(0)	0 (1)	0.003	1 (0)	0 (1)	0.007

Data are median and range. *P* values of changes between 0 to 6 and 7 months to 3 years in each group (Wilcoxon signed-rank test). No statistically significant differences were observed between the placebo and the ZOL patients at three years.

mineralization and preserve the trabecular calcium content [9]. In that study, BMD at the femoral neck decreased in the placebo group but was unchanged in the ZOL group. The ZOL therapy led to an increase of BMD in the lumbar spine but remained unchanged in the placebo group. Serologic markers of bone turnover were significantly lower in the ZOL-treated patients throughout the six months of the trial. Renal transplant function was not affected by bisphosphonate therapy.

The present study was performed to elucidate whether these two doses of ZOL within the first three months after transplantation exerted long-term beneficial effects on bone mineralization and turnover. For this purpose, all subjects received BMD measurements and determination of serologic markers of bone turnover roughly three years after transplantation.

METHODS

Study design and patients

Twenty patients from the University of Vienna Medical School were randomized to receive either two doses of 4 mg zoledronic acid (ZOL, Novartis, Basel, Switzerland) or placebo at week two and month three after successful cadaveric renal transplantation. The study design, inclusion and exclusion criteria, subjects' demographic and baseline characteristics, were described in detail previously [9]. In brief, patients receiving their first or second cadaveric renal allograft were enrolled into the study if they were normocalcemic and their renal transplant function at two weeks was sufficient (i.e., serum creatinine <2 mg/dL) to allow bisphosphonate therapy. Patients were considered eligible for study participation if baseline bone biopsy obtained during the transplant surgery revealed no sign of adynamic bone disease despite low intact parathyroid hormone (iPTH) levels. The post-transplant immunosuppressive regimen consisted uniformly of corticosteroids, mycophenolate mofetil, and cyclosporine-Neoral (CSA). All patients received 1000 mg of daily calcium citrate in the first six months, but no 1,25$(OH)_2$ vitamin D_3 supplementation. Patients were followed-up for almost three years after transplantation. The median follow-up was 32 (11) months in the ZOL and 33 (11) months in the placebo group. One dropout occurred in the ZOL group because the patient refused to attend the study follow-up visit at year three. Therefore, a complete analysis of nine ZOL patients and all 10 subjects in the placebo group was possible three years after renal transplantation.

The cumulative doses of immunosuppression and other bone-relevant drugs within the first six months and between month six and three years are given in Table 1.

The results of the transiliacal crest biopsy at baseline and at month six were reported previously [9].

Bone mineral density measurements

BMD was determined at baseline, at month six, and at year three. Two different skeletal sites were measured at each time point: lumbar spine at L1-L4 and the femoral neck. Dual-energy x-ray absorptiometry (DEXA) and a QDR-4500 scanner (Hologic, Waltham, MA, USA) were used following the manufacturer's recommendations. The results were expressed as z-scores.

Biochemical markers of bone metabolism

Biochemical markers of bone metabolism were determined at the same time points that densitometry was performed. Markers for osteoclast differentiation or inhibition included osteoprotegerin, c-telopeptide of type I collagen, calcitonin and intact parathyroid hormone (iPTH). Biochemical indicators of osteoblast activity were osteocalcin and bone-specific alkaline phosphatase. Osteoprotegerin was determined by enzyme-linked immunosorbentassay (ELISA), bone-specific alkaline phosphatase by electrophoresis, 1,25$(OH)_2$ vitamin D_3 by radioimmunoassay, and all others by electrochemoluminescence techniques.

Statistical analysis

The sample size calculation was reported elsewhere [9]. Because data were not normally distributed, values are presented as median and range. Between-group differences were evaluated by using the Mann-Whitney-U

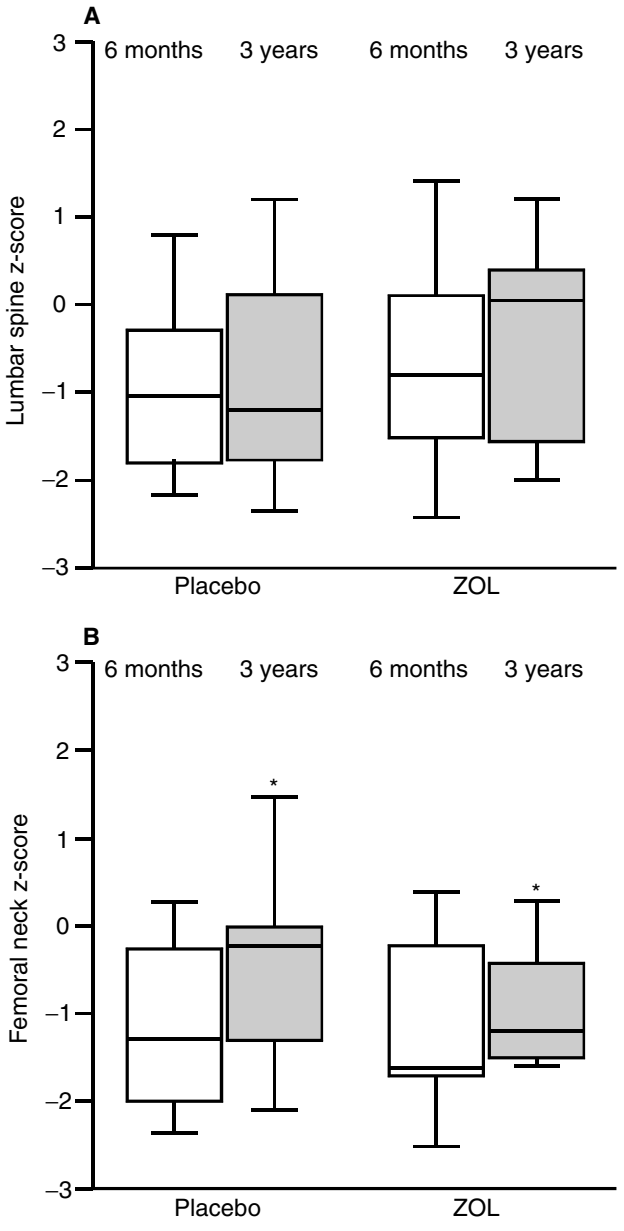

Fig. 1. Box-and-whisker plots of bone mineral densitometry measurements of lumbar vertebrae and femoral neck at six months (open boxes) and three years (gray boxes) after renal transplantation. The horizontal lines in the boxes denote the 25th, 50th (median), and 75th percentile values; the end of the whiskers denote the minimum and maximum values within 1.5 times the interquartile range from the 25th and 75th percentile values. No outliers are present. Patients were randomly treated with either two doses of 4 mg zoledronic acid (ZOL, $N = 9$) or placebo ($N = 10$) at week two and month three after transplantation. Both patient groups exhibited a statistically significant increase of femoral neck z-scores but not in the lumbar spine. No between-group differences were observed. $^*P < 0.05$ month 6 vs. year 3 after transplantation. (Wilcoxon signed-rank test: ZOL, $P = 0.044$; placebo, $P = 0.021$).

test, within-group differences by the Wilcoxon signed-rank test.

$P < 0.05$ was considered statistically significant. The SPSS software version 11.0.1 was used for analysis (SPSS, Inc., Chicago, IL, USA). The study was approved by the local Ethical Committee of the University of Vienna, and subjects gave their informed written consent (EK 99/206; to be found at http://ohrp.cit.nih.gov/search/asearch.asp).

RESULTS

Bone mineral density

BMD of the femoral neck increased statistically significant in both groups from month six to year three after transplantation. The increase in BMD z-scores of the lumbar spine in the same time interval, however, did not reach statistical significance in the ZOL group and was unchanged in the placebo group (Fig. 1). The median z-scores were around –1 in the lumbar spine and around –1.5 in the femoral neck region at month six after transplantation, suggesting no severe demineralization of bone. Despite the relatively high baseline values for renal transplant patients, mineralization of cancellous bone increased in both treatment arms. No statistically significant differences could be detected between the treatment groups at any time after transplantation.

Two incidental vertebral compression fractures occurred in each treatment group between month six and year three after engraftment.

Biochemical markers of bone turnover

Biochemical markers of bone disease and serum creatinine split by treatment group are given in Table 2. Renal allograft function was good in both treatment groups at month six and did not markedly deteriorate over the follow-up period. It is of note that subjects with a serum creatinine above 2 mg/dL two weeks after transplantation were considered ineligible for bisphosphonate therapy and thus were not enrolled into the study.

Markers of osteoclast activity. Osteoprotegerin, which inhibits osteoclast differentiation/maturation and activity was statistically higher at month six after transplantation in the ZOL group compared with the placebo group ($P = 0.035$). The inhibitory effect of the bisphosphonate on osteoclastic activity ceased thereafter and osteoprotegerin returned to similar levels as observed in the placebo group. Accordingly, c-telopeptide, which is a marker of osteoclast activity, was suppressed at month six in the ZOL group compared with the placebo group ($P = 0.028$). C-telopeptide levels increased thereafter toward values that were observed in the placebo group. Calcitonin, an inhibitor of osteoclast activity, and iPTH, an osteoclast activator, nearly normalized within the first months after transplantation, not being different within and between groups from month six to year three. Especially the secondary hyperparathyroidism at transplantation almost completely reversed within the first months of proper renal allograft function. Accordingly, adequate conversion of $24,25(OH)_2$ D_3 to bioactive $1,25(OH)_2$ vitamin D_3 occurred within the first six months in both

Table 2. Biochemical bone markers and serum creatinine

	Placebo $N = 10$			ZOL $N = 9$		
	6 months	3 years	*P* value	6 months	3 years	*P* value
Osteoclast differentiation-inhibition						
Osteoprotegerin *pmol/L*	6 (8)	5 (11)	0.91	10 (21)	5 (4)	0.12
C-telopeptide *nmol/L*	7 (12)	6 (11)	0.52	3 (8)	4 (4)	0.40
Calcitonin *pg/mL*	6 (15)	6 (20)	1.00	10 (17)	6 (18)	0.67
iPTH *pg/mL*	80 (162)	96 (369)	0.20	79 (347)	80 (163)	0.52
Vitamin D3 *pg/mL*	22 (79)	28 (67)	0.12	33 (39)	36 (37)	0.50
Osteoblast activity						
Osteocalcin *ng/mL*	43 (80)	57 (218)	0.39	13 (91)	38 (45)	0.19
Bone specific alkaline phosphatase *U/L*	22 (36)	22 (54)	0.75	15 (42)	23 (21)	0.12
Serum calcium *mmol/L*	2.5 (0.4)	2.4 (0.5)	0.19	2.4 (0.7)	2.4 (0.7)	0.78
Serum phosphate *mmol/L*	0.9 (0.8)	1.1 (0.5)	0.06	0.8 (1.1)	1.0 (0.4)	0.16
Serum creatinine *mg/dL*	1.5 (0.8)	1.7 (2.1)	0.20	1.3 (1.2)	1.4 (1.9)	0.31

Data are median and range. *P* values of changes between 6 months and 3 years in each group (Wilcoxon signed-rank test). No statistically significant differences were found between the placebo and ZOL group at three years.

groups and continued to be sufficient within the next years.

Osteoblast metabolism. Osteocalcin, which is a non-collagenous protein that is synthesized by osteoblasts and correlates with bone formation, was suppressed in the ZOL group at month six compared with the placebo group. During the follow-up period, the effects of early ZOL therapy on osteoblast activity obviously ceased and osteocalcin returned to values not different to placebo-treated patients. These data are inversely correlated with the inhibitory effects of ZOL on osteoclasts. The other investigated marker of osteoblast activity, bone-specific alkaline phosphatase, showed identical regulation to osteocalcin. Bone-specific alkaline phosphatase was lower in the ZOL patients at month six and increased thereafter to values not different to the placebo group. Serum calcium and phosphate were similar in both groups at every time point (Table 2).

Acute rejections and bone-affecting medication

In the first six months three biopsy-proven acute rejections, all Banff 2a, occurred in the placebo group, and two in the ZOL group. All rejections were successfully treated with 3 mg/kg/d anti–T-lymphocyte globulin for 10 to 14 days (either ATG-Fresenius, Bad Homburg, Germany or Thymoglobuline-Pasteur Mérieux, Lyon, France). No acute rejections occurred after the first six months, with the exception of one clinically suspected but not biopsy-confirmed rejection in the ZOL group, which was successfully treated with three days of 100 mg dexamethasone. The cumulative corticosteroid dose was not different between the groups, but was statistically significantly higher in the first months after transplantation compared with the time thereafter. The median (range) daily steroid dose at three years was 4 (3) mg in the ZOL and 3 (5) mg in the placebo group respectively ($P = 0.133$). Three patients in each group received lipid-lowering therapy with either 10 or 20 mg of atorvastatin at three years ($P = 1.0$). No between-group differences could be observed in the average dose of loop diuretics or thiazides at any time point. Diuretic use was not different in the first half year than thereafter. The cumulative dose of CSA was equal in both groups, and doses were higher in the first months than thereafter (Table 1).

DISCUSSION

In the present paper we report the three-year follow-up of patients who were randomized to short-term ZOL or placebo treatment. Two doses of 4 mg of ZOL at two weeks and three months prevented bone loss within the first six months after transplantation as evidenced by an increase in trabecular calcium content. Placebo-, but not ZOL-treated patients, lost bone mineral density at femoral neck in the first six months. The BMD of the lumbar spine increased in the ZOL group but remained unchanged in the placebo group in that period. From month six onwards, femoral neck BMD increased in both groups, being statistically higher at three years than at six months. This effect is most likely driven by the resolution of the secondary hyperparathyroidism within the first months after transplantation and by the fact that corticosteroid doses are significantly higher early after transplantation than doses used for maintenance immunosuppression after the first half year. The BMD of lumbar spine at three years was not statistically different to the six-month results in either group; ZOL-treated patients, however, exhibited a trend toward increased BMD compared with six-month readings. The lack of statistical significance might reflect a type two error caused by the low number of patients in our study. This trend toward increased BMD of cancellous bone after ZOL therapy is supported by previous papers using other third-generation bisphosphonates after renal transplantation [10, 11].

As shown in the analysis of biochemical bone markers, iPTH levels regressed to subnormal values within the first months after engraftment and stayed in that range over the next years in the investigated population with good renal allograft function. Osteoprotegerin, also known as

RANK [receptor activator of nuclear factor (NF)-κB], inhibits osteoclast maturation and activity. We recently were able to show in patients undergoing renal transplantation that a combination of low osteoprotegerin and elevated iPTH best predicted morphologic chances of high turnover bone disease and decreased bone mineralization [12]. Osteoprotegerin was significantly elevated and iPTH suppressed at month six in the ZOL group, suggesting adequate osteoclast inhibition by the bisphosphonate. At year three after transplantation, values had returned to their normal/subnormal range in the ZOL group, indicating a nonsustained ZOL effect on osteoclasts.

Osteoblast activity was monitored by sequential determinations of osteocalcin and bone-specific alkaline phosphatase serum levels. Both markers showed a trend, although not statistically significant, toward an increase over time in both groups, suggesting active osteoblastic apposition of mineralized bone, which is reflected by increased femoral BMD at three years.

A recent paper by Fan et al [11] used a similar study protocol to ours. Like their results, we found that patients who received two doses of a third-generation bisphosphonate did not experience significant bone loss in the femoral neck in the early phase after renal transplantation. We could even demonstrate a significant increase in lumbar spine BMD in ZOL-treated patients. In the follow-up study at four years, Fan et al reported a significant loss of femoral neck BMD of 12% in the placebo group. The decrease in lumbar spine BMD averaged 5% but did not reach statistical significance. Pamidronate-treated patients did not experience a statistically significant bone loss, neither at the femoral neck nor at the lumbar spine over the four-year study period. We did not find a long-term effect of short-term bisphosphonate therapy because both groups increased with their femoral neck BMD and exhibited unchanged lumbar spine BMD. A likely explanation is the fact that early bone loss was only moderate in our patients, even in the placebo group. ZOL-treated patients experienced an average loss of only 2.9% of BMD given in g/cm^2 in the femoral neck and improved by roughly 3% in lumbar spine BMD in the first six months [9]. Therefore, no big improvement could be expected long-term after transplantation. The reason for the overall well-preserved mineralization density in our patients is the specific prophylaxis and treatment of emerging and existing pretransplant bone disease, mainly by controlling hyperparathyroidism. Another explanation for the different findings in the studies is the difference in bisphosphonate type and dose. Fan used 0.5 mg/kg pamidronate at transplantation, and at month one we infused 4 mg ZOL twice within three months after engraftment. Direct comparisons of single doses of pamidronate (90 mg) with ZOL (2 and 4 mg) in non-transplant patients with osteolysis showed equal efficacy on hard end points, such as skeletal disease progression to the point where radiation therapy was required [13, 14]. Last but not least, the difference between the two studies might be explained by the loss of 35% of patients during follow-up in the Fan study, whereas only one patient did not complete the three-year follow-up visit in our study.

As indicated by the biochemical resolution of osteoclast inhibition after the first six months in the ZOL group, it may be worth studying if longer-term bisphosphonate therapy exhibits additional beneficial effects to steroid minimization and spontaneous resolution of hyperparathyroidism on BMD long-term after transplantation. Because of the relative lack of published evidence, no clear recommendation currently exists on the use of bisphosphonates long-term after renal transplantation. There is good agreement among researchers that short-term use of new generation bisphosphonates in patients after kidney transplantation with high turnover renal osteodystrophy is beneficial, although studies using hard end points such as fracture rates are missing. The short-term use of bisphosphonates in renal transplant patients with low turnover bone disease is less clear and sometimes even considered a relative contra-indication because of the potential risk of adynamic bone disease. On the other hand, bisphosphonates predominantly inhibit osteoclasts and to a lesser extent osteoblasts. Recent evidence even suggests that bisphosphonates prolong osteoblast survival in glucocorticoid-induced depression of bone formation [15]. Thus, bisphosphonate therapy should lead to a positive bone balance, despite the presence of low bone turnover before transplantation. Indeed, as shown in our previous trial, none of the three subjects with low turnover bone disease at baseline that received low dose bisphosphonate therapy exhibited signs of adynamic bone disease or osteomalacia in the follow-up bone biopsy at six months [9]. Furthermore, low turnover osteodystrophy is often used synonymously with hypoparathyroidism in the absence of morphologic results in renal transplant patients, but recent papers failed to demonstrate a close correlation between serum iPTH levels and histologic readings [12, 16].

Grotz et al [10] recently demonstrated that one year post renal-transplant bone loss can be prevented by ibandronate at months three, six, and nine. Long-term follow-up data on these patients are not available yet, however. According to an earlier paper by Grotz et al [17], in which the authors found that bone loss two years after renal transplantation was not different in the renal transplant population compared with the matched general population, we also found no loss in the lumbar spine BMD at three years after transplantation in either group.

CONCLUSION

We have shown that BMD of cancellous bone improved in ZOL- and placebo-treated renal transplant

patients from month six onward. Resolution of hyperparathyroidism and low maintenance steroid doses are likely to be responsible for this effect. Short-term benefits of ZOL therapy did not result in sustained effects on bone BMD in our renal transplant population with only mild osteopathy.

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